Chapter 5

PREGNANCY

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The reproductive system has been publicized as much as the cardiovascular and central nervous systems as target organs influenced by the carbon monoxide contained in cigarette smoke. Pregnant women are being warned that cigarette smoking causes low birth weight, prematurity and perinatal morbidity and mortality.

Although pregnant women who smoke have a higher incidence of low birth weight infants than nonsmokers, this association is not necessarily one of cause and effect. Since 1972, there have been additional epidemiologic studies which question a causal effect of smoking. Women who smoke are different from nonsmokers in their familial background, nutrition, socio-economic factors and environmental exposures. The details of epidemiologic and environmental studies are reviewed in this chapter, as they relate to low birth weight. Mortality and morbidity statistics of the newborn have been excluded because they are influenced by factors which are remotely related to carbon monoxide contained in cigarette smoke.

A. Carboxyhemoglobin Levels in Pregnancy

The blood levels of carboxyhemoglobin in pregnant women are in the same range of values as in nonpregnant women. For pregnant smokers, the range of values reported by various investigators is as follows:

Investigators (year)	Number Pregnant Women	COHb % Saturation mean ± SD.	(range)
Haddon et al. (1961)[1]	13		(0 - 8.4)
Heron (1962)[2]	21	6.7	(1.6 - 14)
Young and Pugh (1963)[3]	6	2.0±0.7	(1.0 - 3.0)
Younaszai et al. (1968)[4]	16	8.3	(2.0 - 12.0)
Scoppetta (1968)[5]	28	4.5	(0.5 - 15.0)
Baribaud et al. (1970)[6]	27	4.4	
Cole et al. (1972)[7]	93	4.1	(0.5 - 14.0)

The above results show a wide range of values for carboxyhemoglobin in pregnant smokers. Although the mean values are higher than those seen for pregnant nonsmokers (omitted from above table), there is an overlapping in the values for both groups.

1. Fetal Blood.

In most of the studies on maternal blood levels tabulated above, the corresponding fetal blood has been analyzed. The % saturation in the fetal blood is higher than the maternal blood because of the lower hemoglobin values in the former.

significant!

2. Carbon Monoxide Uptake During Smoking.

Pavlou et al.[8] obtained samples before and after smoking cigarettes. The patients showed a steady rise from 1 - 4.2% in the control period to 5.3 - 11.2% at the end of the smoking period. The duration of the change was not followed. These transient changes in the maternal blood are probably not reflected in the fetal blood because of the slow diffusion of carbon monoxide through the placenta.[9-11] The rise in carboxyhemoglobin concentration in response to smoking a single cigarette was compared in pregnant women, pregnant women suffering from anemia, and nonpregnant women. Dow et al.[12] reported the following responses to smoking:

	% CO Hb Mean ± S E		
	Before Smoking	After Smoking	Δ
pregnant (nonanemic)	1.68±0.27	5.55±0.34	3.87
pregnant anemic	1.68±0.2	6.7±0.2	5.0
nonpregnant (nonanemic)	2.24±0.2	4.3±0.19	2.11

The conclusion of Dow et al.[12] is that pregnant women, particularly those suffering from anemia, show a more-pronounced increase in carboxyhemoglobin levels than nonpregnant women. If the implication is that anemia causes an increase in uptake of carbon monoxide, that is fallacious as pointed out by Payne[13] who calculated the absolute concentration from the percentage saturation. The levels are as follows:

	CO Hb in mg/100 l		
	Before Smoking	After Smoking	Δ
pregnant (nonanemic)	203	672	469
pregnant anemic	150	596	446

In the above table, the uptake of carboxyhemoglobin as a result of smoking by anemic pregnant women is no greater than that for nonanemic subjects. When levels of carboxyhemoglobin are expressed in terms of absolute amounts, anemia does not increase the uptake of carbon monoxide in pregnant women.

3. Effect on the Fetus.

Asmussen and Kjeldsen[14] have recently reported their observations on the ultrastructure of umbilical arteries from newborn children. They reported intimal changes seen in the arteries of children of smoking mothers which were not seen in those of nonsmoking mothers. They interpreted these differences as representing early signs of atherosclerosis, similar to those seen in rabbits exposed to carbon monoxide (see Chapter 3).

It should be pointed out that atherosclerosis is not a disease of the newborn and that the umbilical and placental arteries behave differently from the systemic arteries. Kawahara et al.[15] have compared the response of human placenta and systemic blood vessels and noted the opposite effects of vasoconstrictors and vasodilators. Furthermore, the uteroplacental blood pool does not respond in a consistent manner to cigarette smoking. Cloeren et al.[16] reported 5 pregnant women who initially showed a slight decrease followed by an increase whereas in the other five, there was only an increase in the

uteroplacental blood pool following cigarette smoking. This variability is consistent with the proposition that smokers are not a uniform population and that the placental vessels do not behave in a uniform fashion.

4. Role of Nicotine.

There is a change in the fetal breathing movements during maternal smoking.[17] Gennser et al.[17] explain the effect as a result of nicotine that has crossed the placental barrier. Although nicotine has been detected in samples of amniotic fluid, it is not uniformly seen in all smokers. Van Vunakis et al.[18] found nicotine in 22 out of 37 samples in smokers with the following wide distribution of concentration.

No. of Smokers	Range of nicotine ng/ml/amniotic fluid
15	0 - 10
13	11 - 20
8	21 - 30
1	31 - 40

The wide range of nicotine concentration in the amniotic fluid reflects the variability of nicotine absorbed from cigarette smoke among smokers. It is unlikely that a dose response relationship can be derived from amniotic fluid levels and daily consumption of cigarettes.

B. Association of Smoking with Birth Weight

Until 1972, the epidemiologic studies indicated that smoking mothers had newborns of lower birth weight than nonsmoking mothers. The prevalent opinion expressed in the Surgeon General Reports (1967, 1969, 1971, 1972) was that smoking, particularly the elevated carboxyhemoglobin, was the cause of

the low birth weight. The subject has been omitted from the 1973, 1974 and 1975 Reports so that recent events have not been publicized. They are as follows:

1. Examination of Future Smokers Before Acquisition of the Smoking Habit.

In 1972, Yerushalmy[19] explored the question whether "this increase in low birth weight infants to smoking gravidas is due to the smoking or the smoker". Unlike previous epidemiologic studies, Yerushalmy investigated the reproductive performance of future smokers during the periods before they acquired the smoking habit. His conclusion was that women who subsequently became smokers had a high incidence of low birth weight infants during the period before they began to smoke. He questioned the role of smoking as an exogenous factor and proposed instead that the cause of the low birth weight lies in the smoker herself. The results of epidemiologic studies since 1972 have revealed the importance of maternal nutrition which, in turn, influences fetal nutrition.[20-25] Prematurity and low birth weight are seen more frequently in the black group regardless of smoking habit.[26-28] Socioeconomic factors, education, legitimacy, familial trends, ethnic origin and age of the mother influence the perinatal mortality.[29-35] The role of smoking has not been evaluated because of the concurrent risk factors which differ between smokers and nonsmokers. The smoking habit of the father also influences the status of the newborn[36] suggesting that a genetic factor from both parents is transmitted to the offspring which, in turn, influences birth weight and perinatal morbidity and mortality. This subject is

discussed further in Chapter 9. The original study of Yerushalmy in 1972,[19] as well as the subsequent investigations cited above, have led to an exchange of correspondence among investigators,[37-52] The major criticism revealed in published letters is that epidemiologic studies cannot support causal relationships between smoking and low birth weight.

2. Identification of Chemical Factors Influencing the Fetus.

A reduction in birth weight from chronic carbon monoxide poisoning has not been reported. There are no published epidemiologic studies of women exposed occupationally to carbon monoxide. The literature on maternal poisoning indicates death of the fetus with carboxyhemoglobin levels as low as 10% saturation in the mother.[53-61] There is reason to suspect that this level was not the highest amount of carbon monoxide exposure causing fetal death.

In recent years, several chemical factors in the environment have been suspected of causing a reduction in birth weight. They include carbon monoxide and other air pollutants,[62-64] plant constituents that are likely to be ingested,[65] high nitrate content in the water[66] and trace metals in the water, food and atmosphere.[67] Drugs such as salicylates,[68-70] diphenylhydantions,[71] caffeine,[72] alcohol[72-75] and hormones[76-81] have been reported to cause fetal malformations, prematurity and neonatal deaths. These chemical factors have not been considered in the epidemiologic investigation of risk factors (see above).

C. Correlation of Human Studies and Animal Experiments.

In 1972, Astrup et al.[82] reported the results of human and animal studies and concluded that the "carbon monoxide in tobacco smoke might be responsible for the reduced birth weight of babies whose mothers smoked during pregnancy." There are several features in this report which have been overlooked.

1. Variability of Carboxyhemoglobin Levels in Pregnant Women.

Pregnant women in the outpatient clinic of a hospital in Copenhagen were chosen at random and blood samples were taken for carboxyhemoglobin levels. The results indicate a considerable overlapping of values between smokers and nonsmokers:

COHb % Saturation	No. of Pregnant Women	
	Smokers	Nonsmokers
0-1%	336	678
1-2%	155	128
2-3%	139	51
3-4%	105	16
4-5%	50	7
5-6%	21	1
6-7%	11	2
7-8%	2	1
8-9%	4	0
9-10%	1	0
Total	824	884
Mean COHb	1.92%	0.87%

Although the distribution of carboxyhemoglobin values was tabulated, only the mean values for birth weight were mentioned: 2990 g for smokers and 3225 g for nonsmokers. They further stated that, among smokers, there was a "negative correlation between birth weight and mean value of carboxyhemoglobin measurements of each individual."

Astrup et al.[82] did not mention the correlation of birth weight with carboxyhemoglobin measurements of nonsmokers. In the discussion of their results, they were oblivious to the considerable literature on the role of risk factors, particularly of nutrition which was called to their attention by Neale.[83] Subsequent to 1972, the report of Yerushalmy[19] and others appeared invalidating the premise of Astrup et al. that smoking was the cause of the low birth weight.

2. Rabbit Experiments on Carbon Monoxide by Astrup et al.

Astrup et al.[82] exposed rabbits to carbon monoxide continuously for 30 days, from mating until the day before expected delivery. The rabbits that had concentrations of 16 to 18% had 35% stillbirths and offspring which died within the first hour, and lower birth weight than control rabbits. Since the levels of 16 to 18% were never attained in Astrup's patients, these experiments are irrelevant to the human studies.

The next exposure experiments by Astrup et al.[82] consisted of rabbits exposed continuously to carboxyhemoglobin levels of 8 to 9 %. Again, this level was seen only in one out of 824 pregnant women. Astrup et al. did not

report animals exposed to levels of 5% carboxyhemoglobin saturation, which would be relevant to their observations.

3. Experiments by Other Investigators.

Although Astrup et al.[82] reported the results of their rabbit experiments in 1972, there has been no confirmation of their results. To the contrary, there are observations which question the relevance of carbon monoxide experiments to the smoking question. Kirschbaum et al.[84] injected nicotine and administered cigarette smoke to pregnant ewes. Gas exchange and cardiovascular function were unchanged in both the ewes and their fetuses. Chronic exposure to cigarette smoke in mice[85] and rats[86] that were pregnant did not influence birth weight nor induce malformations of fetuses. The experiments showing a reduction in birth weight of newborns of rats exposed to cigarette smoke are explained by a reduction in food intake by the pregnant rats.[87]

D. Practical Aspects of Smoking in Pregnancy

That smoking during pregnancy causes an elevation in carboxyhemoglobin level and reduction in birth weight of the newborn is not supported by experimental and epidemiologic data and indeed is rejected by better-designed studies. Animals exposed to cigarette smoke do not duplicate the results of exposure to carbon monoxide. Furthermore, there is a considerable degree of overlapping of carboxyhemoglobin levels of smoking and nonsmoking women in pregnancy.

Several risk factors in pregnancy have been identified as contributing to the low birth weight of infants of smokers, such as their familial background, nutritional status, socioeconomic factors and environmental exposure to chemicals.

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